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(54) Title: HIV PROTEASE INHIBITOR COMBINATION

(57) Abstract

The combination of the HIV protease inhibitor Compound J and any one or more of four other potent HIV protease inhibitors is useful in the inhibition of HIV protease, the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

TITLE OF THE INVENTION

HIV PROTEASE INHIBITOR COMBINATION

BACKGROUND OF THE INVENTION

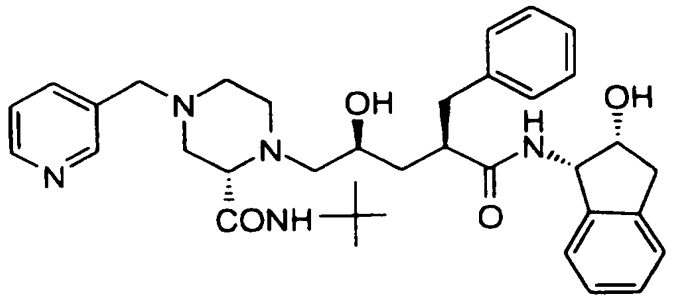
This case is a continuation-in-part of Merck Case 19280, U.S.S.N. 08/289,474, filed August 11, 1994.

This case is related to Merck case 18996, U.S.S.N. 08/059,038, filed May 7, 1993, and 18996IA, U.S.S.N. 08/235,576, filed April 29, 1994.

A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. Inhibition of this processing prevents the production of normally infectious virus. For example, Kohl, N.E. et al., Proc. Nat'l Acad. Sci., 85, 4686 (1988) demonstrated that genetic inactivation of the HIV encoded protease resulted in the production of immature, non-infectious virus particles. These results indicate that inhibition of the HIV protease represents a viable method for the treatment of AIDS and the prevention or treatment of infection by HIV.

Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277 (1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, an endonuclease and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al., Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)].

The Compound J, of the structure:



named N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarbamoyl)-piperazinyl))-pentaneamide, or pharmaceutically acceptable salt thereof, is a potent inhibitor of HIV protease and is useful in the treatment of AIDS or ARC, without substantial side effects or toxicity.

Applicants have discovered that administration of Compound J in combination with other HIV protease inhibitors is useful for the treatment of AIDS or ARC.

Applicants demonstrate that the combination of compounds of this invention is an effective inhibitor of HIV protease.

In the present invention, applicants administer either simultaneously or alternatively the potent HIV protease inhibitor Compound J with one or more of other potent HIV protease inhibitors, such as Compounds I, II, or III, or IV.

BRIEF DESCRIPTION OF THE INVENTION

The combination in this invention is useful in the inhibition of HIV protease, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts (when appropriate), pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or

vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

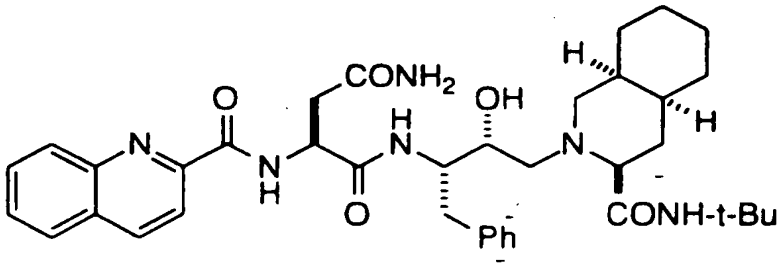
DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

This invention is concerned with the combination of certain compounds, or pharmaceutically acceptable salts thereof, in the inhibition of HIV protease, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune deficiency syndrome (AIDS). The combination is defined as follows:

A combination comprising Compound J and an inhibitor of HIV protease selected from Compounds I, II, III, or IV.

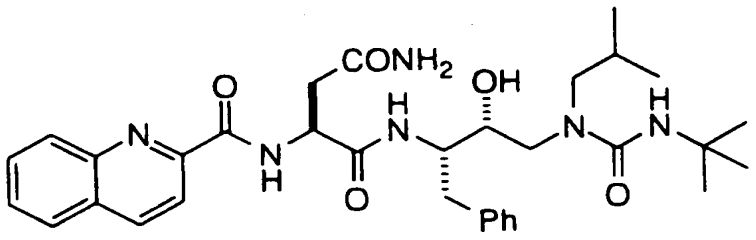
The HIV protease inhibitor Compound J is synthesized by the protocol of Merck Case 18597Y, EP 0541168, published 12 May 1993, herein incorporated by reference. The Compound L-735,524 is N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide, or pharmaceutically acceptable salt thereof.

Compound I is:



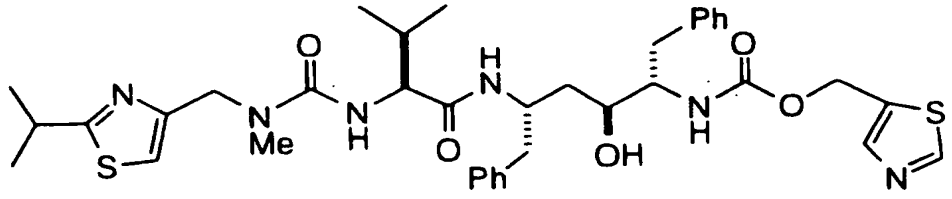
or pharmaceutically acceptable salt thereof. It is synthesized by the procedures of EP 0346847. See also N.A. Roberts et al., Science, 248, 358 (1990).

Compound II is:



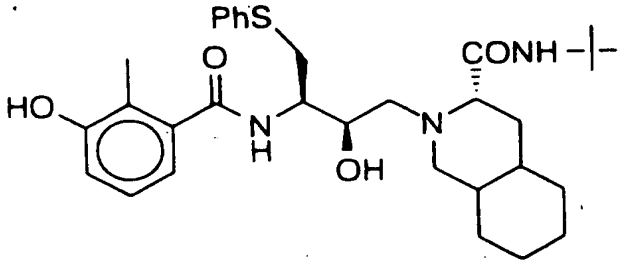
It is synthesized by the procedure of EP 0346847, PCT WO 92/08700 and PCT WO 92/8698.

Compound III is:



or pharmaceutically acceptable salt thereof. It is synthesized by the methods of EP 0486948, and PCT WO 94/14436.

Compound IV is:



or pharmaceutically acceptable salts thereof. It is synthesized by the methods of WO 95/09843.

The pharmaceutically-acceptable salts of the present invention (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

C_{1-4} alkyl esters as prodrugs are included wherever appropriate.

The combination of compounds of the present invention is useful in the inhibition of HIV protease, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC

(AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by, e.g., blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The combinations in this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the combinations in this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the combinations in this invention are useful in establishing or determining the binding site of other antivirals to HIV protease, e.g., by competitive inhibition. Thus the combinations in this invention are commercial products to be sold for these purposes.

For these purposes, the combinations of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of each compound in the combination of the present invention.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets; nasal sprays; sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquidify and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered to humans in the dosage ranges specific for each compound. Compound J or pharmaceutically acceptable salt thereof is administered orally in a dosage range between about 40 mg and about 4000 mg per day, divided

into between one and four doses per day. A preferred oral dosage range for Compound J or pharmaceutically acceptable salt thereof is between about 200 mg and about 1000 mg administered three times per day. Compound I or pharmaceutically acceptable salt thereof is administered orally at a dosage range of between about 100 mg and about 4000 mg per day. A preferred oral dosage range for Compound I or pharmaceutically acceptable salt thereof is between about 200 mg and about 1000 mg administered three times per day. Compound II is administered orally, e.g., as an elixir in 30% ethanol in water, at a dosage range of between about 100 mg and about 4000 mg per day. A preferred oral dosage range for Compound II is between about 200 mg and about 1000 mg administered three times per day. Compound III or pharmaceutically acceptable salt thereof is administered orally at a dosage range of between about 100 mg and about 4000 mg per day. A preferred oral dosage range for Compound III or pharmaceutically acceptable salt thereof is between about 200 mg and about 1000 mg administered three times per day. Compound IV or pharmaceutically acceptable salts thereof is administered orally as a dosage range of between about 100 mg and about 4000 mg per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

EXAMPLE 1

Protocol for Pharmacokinetic Evaluation of Combination Therapy with Only Compound I

This is a multiple-dose, randomized, three-period, crossover-protocol in HIV-infected patients to evaluate the pharmacokinetics and safety of co-administration of Compound J and Compound I.

Twelve HIV-positive patients receive, in randomized order, three different treatments consisting of seven full days of dosing and one additional dose of: active Compound J with Compound I placebo (Treatment A); Compound J placebo with active Compound I (Treatment B); and active Compound J with active Compound I (Treatment C). The treatments are outlined in the following table:

TREATMENT	BOTTLE NUMBER	DRUG	DOSE
A	1	Compound J	600 mg q8h x 22 doses
	2	Compound I placebo	3 capsules q8h x 22 doses
B	1	Compound J placebo	3 capsules q8h x 22 doses
	2	Compound I	600 mg q8h x 22 doses
C	1	Compound J	600 mg q8h x 22 doses
	2	Compound I	600 mg q8h x 22 doses

Compound J is administered as three 200 mg capsules and Compound I as three 200 mg capsules. Placebo capsules match both the active Compound J and the active Compound I.

Compound J or matched placebo is consumed every eight hours. Potential subjects are evaluated for eligibility with a complete history, physical examination (including vital signs with orthostatic signs), 12-lead ECG, and laboratory screening (including a CD4 count) within approximately one month of the study start.

For analysis of safety during each treatment period, blood and urine for laboratory safety tests are obtained and physical examinations performed prior to the first dose (Day 1) and on the last day of dosing (Day 8) of each treatment period. Additionally, 12-lead ECGs are obtained prior to and one hour following the first dose as well as 1 hour following the last dose of each treatment period. Vital signs, including orthostatic signs are measured at frequently scheduled times on the first and last day of dosing. Subjects return on one interim day during the week of dosing (the same day of dosing for each treatment for an individual subject, either Day 3, 4, or 5) for observed dosing, observation for adverse effects, and monitoring of vital signs. Subjects maintain a Diary Card to record the times of ingestion of all doses and note any adverse experiences during each treatment period. A postprotocol evaluation for safety consisting of laboratory safety tests, physical examination, and ECG is performed 24 hours following the final treatment.

During Treatments A, B and C, blood is drawn for determination of plasma concentrations of Compound J and Compound I at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hours following last dose (Day 8). Pharmacokinetic parameters to be analyzed include the maximum plasma concentration and the AUC (area under the concentration-time curve) for each drug.

EXAMPLE 2

Protocol for Combination Therapy with Only Compound I

In this protocol to show the antiviral activity of one regimen of Compound J given with Compound I in HIV-seronegative subjects, Compound J is administered at a dose of 600 mg three times a day and Compound I is administered at 600 mg three times a day. Antiviral activity is measured before and during combination therapy by measuring serum levels of the HIV p24 antigen, serum levels of HIV RNA, and CD4 lymphocyte counts.

EXAMPLE 3

Protocol for Pharmocokinetic Evaluation of Combination Therapy with Only Compound II

This is a multiple-dose, randomized, three-period, crossover-protocol in HIV-infected patients to evaluate the pharmacokinetics and safety of co-administration of Compound J and Compound II.

Twelve HIV-positive patients receive, in randomized order, three different treatments consisting of seven full days of dosing and one additional dose of: active Compound J with Compound II placebo (Treatment A); Compound J placebo with active Compound II (Treatment B); and active Compound J with active Compound II (Treatment C). The treatments are outlined in the following table:

TREATMENT	BOTTLE NUMBER	DRUG	DOSE
A	1	Compound J	600 mg q8h x 22 doses
	2	Compound II placebo	3 capsules q8h x 22 doses
B	1	Compound J placebo	3 capsules q8h x 22 doses
	2	Compound II	600 mg q8h x 22 doses
C	1	Compound J	600 mg q8h x 22 doses
	2	Compound II	600 mg q8h x 22 doses

Compound J is administered as three 200 mg capsules and Compound II as three 200 mg capsules. Placebo capsules match both the active Compound J and the active Compound II.

Compound J or matched placebo is consumed every eight hours. Potential subjects are evaluated for eligibility with a complete history, physical examination (including vital signs with orthostatic signs), 12-lead ECG, and laboratory screening (including a CD4 count) within approximately one month of the study start.

For analysis of safety during each treatment period, blood and urine for laboratory safety tests are obtained and physical examinations performed prior to the first dose (Day 1) and on the last day of dosing (Day 8) of each treatment period. Additionally, 12-lead ECGs are obtained prior to and one hour following the first dose as

well as 1 hour following the last dose of each treatment period. Vital signs, including orthostatic signs are measured at frequently scheduled times on the first and last day of dosing. Subjects return on one interim day during the week of dosing (the same day of dosing for each treatment for an individual subject, either Day 3, 4, or 5) for observed dosing, observation for adverse effects, and monitoring of vital signs. Subjects maintain a Diary Card to record the times of ingestion of all doses and note any adverse experiences during each treatment period. A postprotocol evaluation for safety consisting of laboratory safety tests, physical examination, and ECG is performed 24 hours following the final treatment.

During Treatments A, B and C, blood is drawn for determination of plasma concentrations of L-735,524 and Compound II at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hours following last dose (Day 8). Pharmacokinetic parameters to be analyzed include the maximum plasma concentration and the AUC (area under the concentration-time curve) for each drug.

EXAMPLE 4

Protocol for Combination Therapy with Only Compound II

In this protocol to show the antiviral activity of one regimen of Compound J given with Compound II in HIV-seronegative subjects, Compound J is administered at a dose of 600 mg three times a day and Compound II is administered at 600 mg three times a day. Antiviral activity is measured before and during combination therapy by measuring serum levels of the HIV p24 antigen, serum levels of HIV RNA, and CD4 lymphocyte counts.

EXAMPLE 5

Protocol for Pharmacokinetic Evaluation of Combination Therapy with Only Compound III

This is a multiple-dose, randomized, three-period, crossover-protocol in HIV-infected patients to evaluate the pharmacokinetics and safety of co-administration of Compound J and Compound III.

Twelve HIV-positive patients receive, in randomized order, three different treatments consisting of seven full days of dosing and one additional dose of: active Compound J with Compound III placebo (Treatment A); Compound J placebo with active Compound III (Treatment B); and active Compound J with active Compound III (Treatment C). The treatments are outlined in the following table:

TREATMENT	BOTTLE NUMBER	DRUG	DOSE
A	1	Compound J	600 mg q8h x 22 doses
	2	Compound III placebo	3 capsules q8h x 22 doses
B	1	Compound J placebo	3 capsules q8h x 22 doses
	2	Compound III	600 mg q8h x 22 doses
C	1	Compound J	600 mg q8h x 22 doses
	2	Compound III	600 mg q8h x 22 doses

Compound J is administered as three 200 mg capsules and Compound III as three 200 mg capsules. Placebo capsules match both the active Compound J and the active Compound III.

Compound J or matched placebo is consumed every eight hours. Potential subjects are evaluated for eligibility with a complete history, physical examination (including vital signs with orthostatic signs), 12-lead ECG, and laboratory screening (including a CD4 count) within approximately one month of the study start.

For analysis of safety during each treatment period, blood and urine for laboratory safety tests are obtained and physical examinations performed prior to the first dose (Day 1) and on the last day of dosing (Day 8) of each treatment period. Additionally, 12-lead ECGs are obtained prior to and one hour following the first dose as well as 1 hour following the last dose of each treatment period. Vital signs, including orthostatic signs are measured at frequently scheduled times on the first and last day of dosing. Subjects return on one interim day during the week of dosing (the same day of dosing for each treatment for an individual subject, either Day 3, 4, or 5) for observed dosing, observation for adverse effects, and monitoring of vital signs. Subjects maintain a Diary Card to record the times of ingestion of all doses and note any adverse experiences during each treatment period. A postprotocol evaluation for safety consisting of laboratory safety tests, physical examination, and ECG is performed 24 hours following the final treatment.

During Treatments A, B and C, blood is drawn for determination of plasma concentrations of Compound J and Compound III at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hours following last dose (Day 8). Pharmacokinetic parameters to be analyzed include the maximum plasma concentration and the AUC (area under the concentration-time curve) for each drug.

EXAMPLE 6

Protocol for Combination Therapy with Only Compound III

In this protocol to show the antiviral activity of one regimen of Compound J given with Compound III in HIV-seronegative subjects, Compound J is administered at a dose of 600 mg three times a day and Compound III is administered at 600 mg three times a day. Antiviral activity is measured before and during combination therapy by measuring serum levels of the HIV p24 antigen, serum levels of HIV RNA, and CD4 lymphocyte counts.

EXAMPLE 7

Protocol for Pharmacokinetic Evaluation of Combination Therapy with Only Compound IV

This is a multiple-dose, randomized, three-period, crossover-protocol in HIV-infected patients to evaluate the pharmacokinetics and safety of co-administration of Compound J and Compound IV.

Twelve HIV-positive patients receive, in randomized order, three different treatments consisting of seven full days of dosing and one additional dose of: active Compound J with Compound IV placebo (Treatment A); Compound J placebo with active Compound IV (Treatment B); and active Compound J with active Compound IV (Treatment C). The treatments are outlined in the following table:

TREATMENT	BOTTLE NUMBER	DRUG	DOSE
A	1	Compound J	600 mg q8h x 22 doses
	2	Compound IV placebo	3 capsules q8h x 22 doses
B	1	Compound J placebo	3 capsules q8h x 22 doses
	2	Compound IV	600 mg q8h x 22 doses
C	1	Compound J	600 mg q8h x 22 doses
	2	Compound IV	600 mg q8h x 22 doses

Compound J is administered as three 200 mg capsules and Compound IV as three 200 mg capsules. Placebo capsules match both the active Compound J and the active Compound IV.

Compound J or matched placebo is consumed every eight hours. Potential subjects are evaluated for eligibility with a complete history, physical examination (including vital signs with orthostatic signs), 12-lead ECG, and laboratory screening (including a CD4 count) within approximately one month of the study start.

For analysis of safety during each treatment period, blood and urine for laboratory safety tests are obtained and physical examinations performed prior to the first dose (Day 1) and on the last day of dosing (Day 8) of each treatment period. Additionally, 12-lead

ECGs are obtained prior to and one hour following the first dose as well as 1 hour following the last dose of each treatment period. Vital signs, including orthostatic signs are measured at frequently scheduled times on the first and last day of dosing. Subjects return on one interim day during the week of dosing (the same day of dosing for each treatment for an individual subject, either Day 3, 4, or 5) for observed dosing, observation for adverse effects, and monitoring of vital signs. Subjects maintain a Diary Card to record the times of ingestion of all doses and note any adverse experiences during each treatment period. A postprotocol evaluation for safety consisting of laboratory safety tests, physical examination, and ECG is performed 24 hours following the final treatment.

During Treatments A, B and C, blood is drawn for determination of plasma concentrations of Compound J and Compound IV at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 and 8 hours following last dose (Day 8). Pharmacokinetic parameters to be analyzed include the maximum plasma concentration and the AUC (area under the concentration-time curve) for each drug.

EXAMPLE 8

Protocol for Combination Therapy with Only Compound IV

In this protocol to show the antiviral activity of one regimen of Compound J given with Compound IVin HIV-seronegative subjects, Compound J is administered at a dose of 600 mg three times a day and Compound IV is administered at 600 mg three times a day. Antiviral activity is measured before and during combination therapy by measuring serum levels of the HIV p24 antigen, serum levels of HIV RNA, and CD4 lymphocyte counts.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptions, or modifications, as come within the scope of the following claims and its equivalents.

WHAT IS CLAIMED IS:

1. A combination of compounds, which comprises Compound J and one of either Compound I, II, III, or IV, or pharmaceutically acceptable salt.

2. The combination of compounds of Claim 1, which comprises Compound J and Compound I.

3. The combination of compounds of Claim 1, which comprises Compound J and Compound II.

4. The combination of compounds of Claim 1, which comprises Compound J and Compound III.

5. The combination of compounds of Claim 1, which comprises Compound J and Compound IV.

6. A method of inhibiting HIV protease, comprising administering to suitable mammal in need of such treatment an effective amount of the compounds in any combination according to Claim 1.

7. A method of preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC, comprising administering to a suitable mammal in need of such treatment an effective amount of the compounds in any combination according to Claim 1.

8. A pharmaceutical composition useful for inhibiting HIV protease, comprising an effective amount of the compounds in any combination according to Claim 1, and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition useful for preventing or treating infection of HIV or for treating AIDS or ARC, comprising an effective amount of the compounds in any combination according to Claim 1, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/09956

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/495 A61K31/435 A61K31/425 //(A61K31/495,31:47), (A61K31/495,31:435),(A61K31/495,31:425)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,94 14436 (ABBOTT LAB) 7 July 1994 cited in the application see page 173, paragraph 8 - page 176, paragraph 4 ---	1,4,6-9
Y	EP,A,0 486 948 (ABBOTT LAB) 27 May 1992 cited in the application see page 143, line 8 - page 144, line 11 ---	1,4,6-9
Y	WO,A,92 08698 (MONSANTO CO) 29 May 1992 cited in the application see page 129, line 8-33 ---	1,3,6-9
Y	WO,A,92 08700 (MONSANTO CO) 29 May 1992 cited in the application see page 127, line 25 - page 128, line 13 --- -/--	1,3,6-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 January 1996	19.01.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Leherte, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 346 847 (HOFFMANN LA ROCHE) 20 December 1989 cited in the application see page 13, line 56	1,2,6-9
Y	EP,A,0 541 168 (MERCK & CO INC) 12 May 1993 cited in the application see page 46, line 27 - line 34	1-9
Y	PROC NATL ACAD SCI, 26 April 1994 USA, pages 4096-4100, VACCA JP; DORSEY BD; SCHLEIF WA; LEVIN RB; MCDANIEL SL; DARKE PL; ZUGAY J 'L-735,524: an orally bioavailable human immunodeficiency virus type 1' see page 4099, column 2, paragraph 3	1-9

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/US95/09956

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 6-7 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ternal Application No
PCT/US 95/09956

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9414436	07-07-94	AU-B-	1492795	15-06-95
		AU-B-	659575	18-05-95
		AU-B-	5954694	19-07-94
		CA-A-	2135890	07-07-94
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		WO-A-	9309096	13-05-93
		ZA-A-	9208563	05-05-93

INTERNATIONAL SEARCH REPORT

In. .ational application No.
PCT/US94/10862

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C12Q 1/68; 1/70; C07H 17/08
US CL :435/5, 6; 536/6.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/5, 6; 536/6.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PAS, Dialog, NTIS, Biosis, Medline
Search terms: FK506, hepatitis D virus, inhibit, macrolide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5,238,689 (DWYER ET AL.) 24 August 1993, see entire document, particularly Column 1.	1-8
A,P	US, A, 5,308,847 (CALNE) 03 MAY 1994, see entire document.	1-8

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 13 NOVEMBER 1994	Date of mailing of the international search report 06 JAN 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer DAVID GUZO Telephone No. (703) 308-0196

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